Title: Dystrophinopathies *GeneReview* – Corticosteroid Therapy
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Corticosteroid Therapy in DMD

Prednisone. It is hypothesized that prednisone/prednisolone has a stabilizing effect on membranes and perhaps an anti-inflammatory effect:

- In a randomized double-blind six-month trial, prednisone administered at a dose of either 0.75 mg/kg/day or 1.5 mg/kg/day increased strength and reduced the rate of decline in males with DMD [Mendell et al 1989].
- In two successive six-month trials of prednisone therapy, improvement began within ten days of starting the treatment, required a single dose of 0.75 mg/kg/day of prednisone for maximal improvement, reached a plateau after three months, and was sustained for as long as three years in those children maintained on doses of 0.5 and 0.6 mg/kg/day [Fenichel et al 1991].
- One open-label study suggested that therapy with prednisone could prolong ambulation by two years. Side effects include weight gain (>20% of baseline) (in 40%), hypertension, behavioral changes, growth retardation, cushingoid appearance (in 50%), and cataracts [Mendell et al 1989, Griggs et al 1993].

Follow-up studies showed that a dose of 0.75 mg/kg/day was more beneficial than a dose of 0.3 mg/kg/day [Fenichel et al 1991]. However, a subsequent study proved the effectiveness of lower doses of prednisolone (0.35 mg/kg/day) in both DMD and BMD. One of the authors noted sustained effectiveness with doses initiated at 0.75 mg/kg/day (maximum daily dose: 40 mg) and gradually reduced (usually because of advancing age and weight gain) to as low as 0.4 mg/kg/day. At lower doses of 0.3 mg/kg/day, the improvement is less robust [Darras, personal communication].

Alternate-day dosing and intermittent dosing (e.g., 10 days "on," 10 or 20 days "off") are also used.

- A study showed reduced incidence of side effects by high-dose (5 mg/kg), twice-weekly dosing [Connolly et al 2002].
- A randomized, crossover, controlled trial of intermittent prednisone (0.75 mg/kg/day) therapy (prednisone or placebo) during the first ten days of each month for six months showed that prednisone slowed deterioration of muscle function in individuals with DMD [Beenakker et al 2005]; side effects did not negatively affect quality of life.
- Similar conclusions regarding the effect and side-effect profile of prednisone treatment for DMD were reached by a Cochrane systematic review [Manzur et al 2004, Manzur et al 2008] and also by the 124th European Neuromuscular Centre workshop on the treatment of DMD [Bushby et al 2004].

- High-dose weekly prednisone, 5 mg/kg, given each Friday and Saturday (total 10 mg/kg/week) can be considered as an alternative to daily treatment in males on a daily regimen with excessive weight gain and behavioral issues [Bushby et al 2010].

Whether the improvement seen in individuals with DMD treated with prednisone is the result of an immunosuppressive effect remains unclear, as individuals treated with azathioprine did not have a beneficial effect.

Deflazacort, a synthetic derivative of prednisolone used in Europe but not currently available in all countries (e.g. U.S.A.), is thought to have fewer side effects than prednisone, particularly with regard to weight gain [Angelini 2007]. A larger study comparing deflazacort to prednisone, carried out in Europe, showed that the two medications were similarly or equally effective in slowing the decline of muscle strength in DMD. Another European multicenter, double-blind, randomized trial of deflazacort versus prednisone in DMD showed equal efficacy in improving motor function and functional performance [Bonifati et al 2000]. A more recent study of deflazacort treatment showed efficacy in preserving pulmonary function as well as gross motor function [Biggar et al 2006].

In a comparison of two different protocols of deflazacort treatment in DMD, a 0.9-mg/kg/day dose was more effective than a dose of 0.6 mg/kg/day for the first 20 days of the month and no deflazacort for the remainder of the month [Biggar et al 2004]; 30% of children on the highest dose developed asymptomatic cataracts that required no treatment. A systematic review and meta-analysis of 15 studies showed that deflazacort improved strength and motor function more than placebo; whether it has a benefit over prednisone on similar outcomes remains unclear [Campbell & Jacob 2003]. Despite the lack of conclusive evidence for superiority of deflazacort over prednisone in the area of effectiveness [Moxley et al 2005], some experts believe that the more favorable side-effect profile (particularly with regard to weight gain) associated with deflazacort makes it a better choice than daily treatment with prednisone.

Initiation and length of treatment. Data regarding the optimal age to begin treatment with corticosteroids or the optimal duration of such treatment are insufficient. It has been proposed that individuals with DMD begin treatment with low-dose prednisone as soon as the diagnosis is made (age 2-5 years) [Merlini et al 2003]; however, large-scale controlled trials to study the efficacy and safety of corticosteroid therapy in early DMD have yet to be conducted. A large, NIH-funded multicenter blind randomized trial (FOR DMD) comparing the efficacy, tolerability, and side effects of three regimens (prednisone 0.75 mg/kg/day, prednisone 0.75 mg/kg/day switching between ten days on and ten days off treatment, and deflazacort 0.9 mg/kg/day) is currently being conducted in young (4- to 7-year-old) steroid-naïve children with DMD. Thus, at this point corticosteroid therapy remains the treatment of choice for affected individuals between ages five and 15 years. Corticosteroid therapy is not recommended in children under age two years [Bushby et al 2010].

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